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(54) Title: USE OF CHOLINESTERASE INHIBITOR FOR TREATING DISEASES ASSOCIATED WITH PROTEOLYTIC ENZYME ACTIVITY			
(57) Abstract The invention relates to the use of a pharmaceutically acceptable cholinesterase inhibitor or a pro-drug therefor in the manufacture of a medicament for combatting diseases associated with proteolytic enzyme activity, such as psoriasis, osteoarthritis, rheumatoid arthritis, Crohn's disease and Ulcerative Colitis.			

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USE OF CHOLINESTERASE INHIBITOR FOR TREATING DISEASES ASSOCIATED WITH PROTEOLYTIC ENZYME ACTIVITY

5 The present invention relates to a method of therapy. In particular the invention relates to a method of combatting diseases associated with elevated levels of proteolytic enzymes.

10 Proteolytic enzymes have been found to play a role in a variety of diseases. These include skin diseases such as psoriasis, osteoarthritis, rheumatoid arthritis, other forms of arthritis, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, chronic obstructive pulmonary diseases, amyloidosis, emphysema and certain cancers such as cancer of the pancreas, 15 breast and colon. Despite what might be perceived as an extremely diverse range of symptoms exhibited by patients suffering from these diseases, they are all characterised by the underlying involvement of proteolytic enzymes.

20 We have developed a new therapeutic method capable of combatting any of these diseases.

Thus we have surprisingly found that cholinesterase inhibitors such as galantamine can effectively combat diseases associated with proteolytic enzymes at the 25 affected body site.

According to one aspect, the present invention provides a method of combatting diseases associated with proteolytic enzyme activity comprising administering to a subject a pharmaceutically acceptable cholinesterase 30 inhibitor.

According to a related aspect, the invention provides the use of a pharmaceutically acceptable cholinesterase inhibitor in the manufacture of a medicament for combatting diseases associated with 35 proteolytic enzyme activity.

As used herein the term 'combatting' includes both therapy and prophylaxis.

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Without wishing to be bound by theory, it is believed that the acetylcholinesterase inhibitors act to block or inhibit the protease activity. This belief is based on our findings that in joint diseases such as osteoarthritis and rheumatoid arthritis, where increased protease activity in synovial fluid is well established, there is an increase in acetylcholinesterase levels, and that treatment with acetylcholinesterase inhibitors such as galantamine has been found useful in counteracting the symptoms associated with joint diseases. It is believed that in such treatment of joint diseases the proteolytic activity is associated with acetylcholinesterase and that the acetylcholinesterase inhibitor is acting to block or inhibit proteolytic activity. It is further believed that the proteolytic activity in other diseases is associated with acetylcholinesterase and that such acetylcholinesterase inhibitors will likewise act to block or inhibit proteolytic activity and thereby counteract the symptoms of other diseases associated with proteolytic enzyme activity.

It is well established that proteolytic enzyme activity plays a role in diseases such as psoriasis, Crohn's disease and ulcerative colitis. Thus collagenase is known to be associated with the inflammatory bowel diseases ulcerative colitis and Crohn's disease, PMN protease is associated with psoriasis, elastase with psoriasis and ulcerative colitis, proteinase 3 and plasminogen activator with psoriasis.

Psoriasis is one example of a disease where proteolytic enzyme activity play a role. Psoriasis is an inflammatory skin disease which can effect all age groups. It is characterised by redness and scaly patches over the skin surface. The disfiguration which results can cause considerable distress to the sufferer, with implications on all aspects of daily life.

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Current therapeutic approaches aim to reduce epidermal cell turnover and thereby control the skin lesions without causing damage to the skin or to other organs. There is no known cure. Treatment by drugs
5 generally involves topical application to the affected sites(s). Topical steroids have been used extensively however long term use of steroids is limited by the skin atrophy which occurs and is not recommended. Other
10 topical agents include tar and dithranol but these have the disadvantage that they cause staining of the skin and are cosmetically unacceptable. Systemic therapies generally used for severe psoriasis include the
15 antimitotic agent methotrexate, which has serious side effects of liver damage, and retinoic acid, which is teratogenic. All existing therapeutic approaches are thus unsatisfactory and there is a need for a new method of combatting psoriasis. The present invention provides such a method.

Thus in a further aspect, the invention provides a
20 method of combatting psoriasis comprising administering to a subject a pharmaceutically acceptable cholinesterase inhibitor.

According to a related aspect, the invention provides the use of a pharmaceutically acceptable
25 cholinesterase inhibitor in the manufacture of a medicament for combatting psoriasis.

Arthritic diseases, such as osteoarthritis and rheumatoid arthritis are also examples of diseases where proteolytic enzyme activity plays a role, as are other
30 rheumatoid diseases such as Juvenile Arthritis, Systemic Lupus Erythematosus, Sjögren's Syndrome, Progressive Systemic Sclerosis, Polymyositis, Dermatomyositis, Ankylosing Spondylitis, Reiter's Syndrome, Psoriatic Arthritis, Relapsing Polychondritis, Relapsing
35 Panniculitis, Crohn's Disease, Ulcerative Colitis, Hereditary Complement Deficiencies, Collagen Vascular Diseases, Felty's Syndrome, rheumatological

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manifestations associated with bacterial and viral endocarditis or myocarditis and other rheumatological manifestations such as anaemia of chronic disorders.

5 The invention also relates to a novel method of treatment or prophylaxis of such diseases and manifestations. The method comprises administering a pharmaceutically acceptable cholinesterase inhibitor.

10 As used herein, the term "rheumatoid" covers any of a variety of disorders marked by degeneration or metabolic derangement of the connective tissue structures of the body, especially the joints and related structures, including muscles, bursae (synovial membranes), tendons and fibrous tissue. They are attended by pain, stiffness, or limitation of motion of
15 these parts. Rheumatoid Arthritis is a chronic, recurrent systemic inflammatory disease primarily of the joints, usually polyarticular, marked by inflammatory changes in the synovial membranes and articular structures and by atrophy and rarefaction of the bones.
20 In late stages deformity and ankylosis develop. Extra-articular manifestations include vasculitis, atrophy of the skin and muscle, subcutaneous nodules, lymphadenopathy, splenomegaly, leukopaenia and often chronic anaemia.

25 In one important embodiment of the invention, the arthritic disorder is osteoarthritis. Osteoarthritis is a chronic degenerative disease of skeletal joints, which affects specific joints, commonly knees, hips, hand joints and spine, in adults of all ages. Osteoarthritis
30 is characterized by a number of the following manifestations including degeneration and thinning of the articular cartilage with associated development of "ulcers" or craters, osteophyte formation, hypertrophy of bone at the margins, and changes in the synovial
35 membrane and enlargement of affected joints. Furthermore, osteoarthritis is accompanied by pain and stiffness, particularly after prolonged activity.

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The method of the invention results in the treatment or prevention of one or several of the following symptoms or signs associated with the above-mentioned diseases: muscle pain, muscle weakness, muscle stiffness, joint stiffness, joint pain, joint or tissue swelling, inflammation, and extra-articular manifestation as mentioned above, including anaemia.

The invention is based on discoveries made in connection with the treatment of patients for other conditions, e.g. chronic fatigue syndrome.

Surprisingly, it was found that patients who, in addition to fibromyalgia or chronic fatigue syndrome, suffered from osteoarthritis or rheumatoid arthritis, had improvement of their arthritis symptoms.

Thus, ten patients with rheumatoid arthritis were treated with galantamine. The purpose of the treatment was to treat their fatigue syndrome resulting from their rheumatoid arthritis. However, it was found that not only did the ten patients improve with respect to their fatigue syndrome, but also in the symptoms of their rheumatoid arthritis condition itself. They had less articular pain and the inflammatory process was less active (as evidenced by less swollen and less painful joints) while they were on treatment with galantamine.

In other studies, reported in detail below, patients suffering from rheumatoid arthritis, osteoarthritis and other rheumatoid diseases, respectively, experienced marked improvements of their condition, e.g. with respect to tiredness, pain, stiffness and grip strength, upon treatment with galantamine.

It was also found by direct measurement that there is a considerable acetylcholinesterase activity in the synovial fluid of patients with rheumatological conditions. This finding is new and may shed light on the clinical observations with galantamine in rheumatological patients as this acetylcholinesterase

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activity is believed to exert a proteolytic activity in the synovial fluid of these patients and may be directly related to tissue damage seen in both rheumatoid diseases and in osteoarthritis.

5 Patients with rheumatoid diseases or other chronic diseases very often suffer from anaemia of unknown pathophysiology. It is a normochromic, normocytic or hypochromic, non-progressive anaemia - the severity being related to the severity of the chronic disease.

10 Both the serum iron and total iron binding capacity are reduced. The serum ferritin is normal or elevated and bone marrow storage iron is normal but erythroblast iron is reduced. The pathogenesis of this anaemia appears to be related to the decreased release of iron from

15 macrophages, reduced cell lifespan and inadequate erythropoietin response to the anaemia. This anaemia is normally only corrected by successful treatment of the underlying disease and does not respond to iron therapy despite the low serum iron.

20 Thus the present invention relates to the use of cholinesterase inhibitors for the preparation of a medicament for treatment or prophylaxis of anaemia associated with chronic disorders.

The present invention provides a method of treating

25 or preventing arthritic disorders, including osteoarthritis, rheumatoid arthritis and other rheumatoid diseases such as Juvenile Arthritis, Systemic Lupus Erythematosus, Sjögren's Syndrome, Progressive Systemic Sclerosis, Polymyositis, Dermatomyositis,

30 Ankylosing Spondilitis, Reiter's Syndrome, Psoriatic Arthritis, Relapsing Polychondritis, Relapsing Panniculitis, Crohn's Disease, Ulcerative Colitis, Hereditary Complement Deficiencies, Collagen Vascular Diseases, Felty's Syndrome, rheumatological

35 manifestations associated with bacterial and viral endocarditis or myocarditis and other rheumatological manifestations such as anaemia of chronic disorders,

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said method comprising administering to a patient in need thereof an effective amount of a cholinesterase inhibitor.

5 The invention encompasses the use of any cholinesterase inhibitor, provided of course that it is pharmaceutically acceptable.

10 Examples of cholinesterase inhibitors which may be used according to the invention include, but are not limited to, physostigmine, tacrine and tacrine analogues, fasciculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, huperazine, donepezil and pro-drugs of any of these in which the inhibitor is modified in accordance with principles of pro-drug construction known in the art. Examples of such
15 modifications include the introduction of hydrophilic or lipophilic groups to enhance solubility, or penetration through cell membranes, respectively.

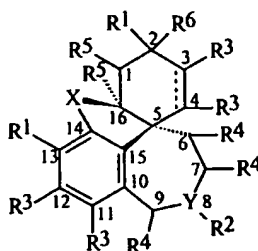
20 Preferred cholinesterase inhibitors for use according to the invention are acetylcholinesterase inhibitors particularly those which are capable of crossing the blood brain barrier.

25 Particularly preferred cholinesterase inhibitors for use according to the invention include galantamine, epigalantamine and norgalantamine, and analogues, salts and derivatives of any of these. Galantamine was previously known as galantamine. It is a tertiary alkaloid which can be extracted from various snowdrop bulbs e.g. the Caucasian snowdrop galanthus woronowii (Amaryllidaceae) and related species and
30 daffodil bulbs or made by chemical synthesis. It has a high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. It is active substantially selectively at nicotinic receptor sites with substantially little effect on muscarinic receptor
35 sites.

Particularly preferred cholinesterase inhibitors for use in the invention are galantamine and its

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derivatives of formula (I):



10

wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R_1 is independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, C_{1-6} alkoxy, alkylthio, aryloxy, arylthio, R_3 -substituted aryloxy, R_3 -substituted arylthio, aralkoxy, an optionally R_3 -substituted aliphatic or aryl carbamyl group, aralkylthio, R_3 -substituted aralkoxy, R_3 -substituted aralkylthio, aryloxymethyl, R_3 -substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_3 -substituted benzoyloxy, aryloxycarbonyl and R_3 -substituted aryloxycarbonyl,

R_2 is selected from hydrogen, straight or branched chain C_{1-6} alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R_3 -substituted phenyl, alkylphenyl, R_3 -substituted alkylphenyl, heterocyclyl selected from α - or β -furyl, α - or β -thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R' -substituted heterocyclyl, where R' is alkyl or alkoxy,

each R_3 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy,

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alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R_4 is independently selected from hydrogen, halo, trifluoromethyl or C_{1-4} -alkyl,

each R_5 is independently selected from hydrogen or hydroxymethyl,

R_6 is hydrogen or C_{1-6} alkyl, or when R_1 at carbon atom 2 is hydroxyl, R_6 may be a moiety of formula I wherein R_6 is hydrogen and R_1 is a linking bond; or

R_1 at carbon atom 2 and R_6 may jointly form semicarbazone,

X is oxygen or NR_3 ,

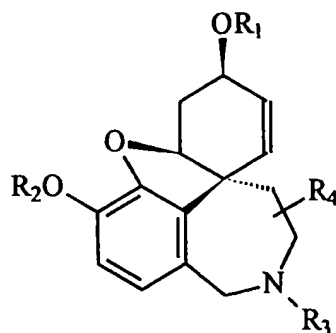
Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and pharmaceutically acceptable acid addition salts thereof.

Of the compounds of formula I which may be used in the method of the invention, preferred compounds are those in which the alkyl moieties contain 1 to 8 carbon atoms, halogen atoms are preferably fluorine, bromine, chlorine, aryl moieties are preferably phenyl, cycloalkyl groups are preferably 3- to 7-membered rings, especially cyclopropyl or cyclobutyl, acyl groups are preferably lower alkanoyl groups and heteroaryl moieties are preferably 5- to 8-membered rings, e.g., thienyl, furyl, pyridyl, pyrrolyl, or pyrizanyl.

Preferred compounds of formula I are the compounds of formula II

- 10 -



wherein R¹ and R² which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

R³ is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

R⁴ represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton,

and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

Formula II includes galantamine itself.

Particularly preferred is galantamine itself, and salts thereof such as halides for example galantamine hydrobromide and the use of these compounds in the manufacture of a medicament for combatting diseases associated with proteolytic enzymes provides a further aspect of the invention.

Among these compounds are those described in EP-A-236684 and W088/08708, the disclosures of which are incorporated herein by reference. Galantamine and its derivatives of formula I and II may be prepared by the

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methods described in these publications.

The cholinesterase inhibitors for use in the invention include compounds which are functionally similar to galantamine. These are defined herein as
5 compounds which possess an at least 10-fold selectivity, preferably an at least 20-fold selectivity, more preferably an at least 40-fold selectivity, and most preferably an at least 50 fold selectivity, for acetylcholinesterase as opposed to butyryl-
10 cholinesterase, when measured by the in vitro method of Thomsen and Kewitz: Selective Inhibition of Human Acetylcholinesterase by Galantamine in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990), and T. Thomsen, H. Kewitz and O. Pleul, J. Clin. Chem. Clin.
15 Biochem. 26 469-475 (1988). The in vitro test described by Thomsen and Kewitz in Life Sciences, Vol 46, pp 1553-1558 (1990) is the one referred to herein whenever numeric (10-fold, 20-fold, 40-fold) reference to selectivity for acetylcholinesterase as opposed to
20 butyrylcholinesterase is made. According to Thomsen and Kewitz, galantamine hydrobromide, when tested under the conditions described, shows a 50-fold selectivity; this selectivity value is taken as the "fix-point" whenever in vitro selectivities are discussed herein and could be
25 used, for the purpose of determining the selectivities for other cholinesterase inhibitors, as a calibration value which is the one to establish with galantamine hydrobromide in any repetition of the experiment described by Thomsen and Kewitz. Thus, with reference
30 to this determination method, a preferred acetylcholinesterase inhibitor is one which in the in vitro method described has an at least 10-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, such as an at least 20-fold
35 selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, e.g. an at least 40-fold selectivity for acetylcholinesterase as opposed to

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butyrylcholinesterase. A selectivity test is commercially available (from Sigma Diagnostics).

For use in the method of the invention the cholinesterase inhibitor such as galantamine and derivatives and salts thereof may be formulated according to conventional methods of pharmacy, together where appropriate with one or more pharmaceutically acceptable carriers, excipients or diluents such as, for example, are described in Remingtons Pharmaceutical Sciences. Such formulations may for example take the form of tablets, capsules, solutions, or lozenges, pessaries, creams, suppositories or transdermal formulations such as patches, creams, ointments or lotions, depending upon the administration route to be used, which may include enterally or parenterally, including orally or injection via the intravenous, intramuscular or subcutaneous routes, or intrathecally by means of an implanted device.

Oral and transdermal administration routes are preferred.

Precise dosage rates and regimes will depend upon the individual patient and may be determined by the medical practitioner based on individual circumstances. For oral administration doses may be within the range of 5-100 mg per day, such as 2 to 70 mg per day eg. 10 to 30 mg. For transdermal administration galanthamine may be delivered in equivalent daily doses. For parenteral administration, dosages may be in the range of 0.1 to 100 mg per day, such as 5 to 100 mg per day, e.g. 10 to 50 mg per day, including 5 to 30 mg per day; lower dosages are often preferred.

Galantamine and its acid addition salts form crystals. They are generally only sparingly soluble in water at room temperature; therefore, injectable compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a

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suspension will be employed at a concentration of 0.1-50 mg/ml, such as 1-50 mg/ml, more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, such as 10-30 mg/ml, especially 20-30 mg/ml of galantamine.

5 Cholinesterase inhibitors such as galantamine and salts thereof may be used as the sole drug in the management of diseases associated with proteolytic enzyme activity, or may be used together with other agents useful in managing such diseases.

10 The invention will now be described with reference to the following non-limiting examples.

Example 1

Formulation of tablets containing galantamine

15

Composition of 1 tablet containing 1 mg galantamine

Galantamine hydrobromide	0.001 g
Calcium phosphate	0.032 g
20 Lactose	0.005 g
Wheat Starch	0.0056 g
Microcrystalline Cellulose	0.015 g
Talc	0.0007 g
Magnesium Stearate	0.0007 g

25

Composition of 1 tablet containing 5 mg galantamine

Galantamine hydrobromide	0.005 g
Calcium phosphate	0.024 g
30 Lactose	0.004 g
Wheat Starch	0.004 g
Microcrystalline Cellulose	0.04 g
Talc	0.002 g
Magnesium Stearate	0.001 g

35

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Composition of 1 tablet containing 10 mg galantamine

	Galantamine hydrobromide	0.010 g
	Lactose	0.040 g
5	Wheat Starch	0.0234 g
	Microcrystalline Cellulose	0.0374 g
	Talc	0.0036 g
	Magnesium Stearate	0.0012 g
	Gelatin	0.0044 g

10

Preparation

All the tablets are prepared according to routine tableting procedures.

15

Example 2

Topical Formulations of Galantamine

(i)

	Wool Fat BP	50g
20	Hard Paraffin BP	50g
	Cetostearyl Alcohol BP	50g
	White Soft Paraffin BP	850g
	Galantamine	10g

25

Mix the ingredients, heat gently with stirring until homogeneous and stir until cold. Fill into tubes containing 60g of ointment.

(ii)

30	Cetostearyl Alcohol BP	80g
	Sodium Lauryl Sulphate BP	10g
	White Soft Paraffin BP	150g
	Liquid Paraffin BP	60g
	Phenoxyethanol BP	10g
35	Purified Water BP	690g
	Galantamine	10g

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- Melt the Cetostearyl Alcohol and heat to approximately 95°C. Add the Sodium Lauryl Sulphate, mix, add approximately 1 ml Purified Water, heat to 115°C and maintain at this temperature, stirring vigorously, until frothing ceases and the product is translucent. Cool quickly while adding the White Soft Paraffin and Liquid Paraffin and stir until the product reaches room temperature.
- 10 Dissolve the Phenoxyethanol in the remaining Purified Water with gentle heating. Melt the ointment base from the previous step, add the galantamine and the Phenoxyethanol solution and stir gently until cold.
- 15 Fill into tubes containing 60g of cream.

Example 3

Treatment of patients suffering from psoriasis

- 8 patients with unequivocal recalcitrant plaque type psoriasis are evaluated clinically, and given 15 - 30 mg galantamine daily. At 1, 2 and 4 weeks, the patients are examined and biopsies taken, ultrasound measurements made and a photographic record kept.

Example 4

Test for cholinesterase activity in blood samples

Method

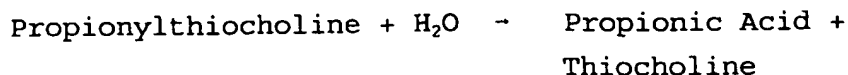
- SIGMA DIAGNOSTICS® CHOLINESTERASE (PTC) kit, available from Sigma Diagnostics, can be used for determining the activity and selectivity of cholinesterase inhibitors. In the following, it is illustrated how the kit is used for the determination of the activity and selectivity of galantamine hydrobromide.

35

Reactions involved in the cholinesterase assay are as follows:

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esterase



- 5 Thiocholine + 5,5'-Dithiobis-2-Nitrobenzoic Acid →
 5-Thio-2-Nitrobenzoic Acid

10 5-Thio-2-Nitrobenzoic Acid is assessed by measuring the
 absorbance at 405 nm. The rate of change in absorbance
 at 405 nm is directly proportional to cholinesterase
 activity.

15 The activity of erythrocyte cholinesterase may be
 calculated on the basis of the measurement of
 butyrylcholinesterase (pseudocholinesterase) in serum
 and cholinesterase in haemolyzed whole blood
 (haemolysate), both measured simultaneously by the
 method described above, and evaluated according to the
 haematocrit value according to the formula

$$20 \quad \text{HChE} = (\text{EChE} \times \text{Hct}^*) + (\text{PChE} \times (1 - \text{Hct}^*))$$

$$25 \quad \text{Therefore, EChE} = \frac{\text{HChE} - (\text{PChE} \times (1 - \text{Hct}^*))}{\text{Hct}^*}$$

* Haematocrit value expressed as decimal equivalent
 (i.e., 44% = 0.44).

30 In the above formulae, EChE is erythrocyte
 cholinesterase activity, PChE is plasma cholinesterase
 activity, HChE is haemolysate cholinesterase activity
 and Hct is haematocrit value of the sample.

35 Another way of assessing the cholinesterase
 activity is to measure the plasma cholinesterase and the
 cholinesterase in purified haemolyzed erythrocytes. By
 doing this, the values are obtained directly.

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Blood samples from 3 patients were tested with the Sigma test. The tests were carried out with samples where no galantamine was added and with samples where 1.25 $\mu\text{g/ml}$ galantamine and 2.5 $\mu\text{g/ml}$ were added in vitro. The results are shown below in table 1.

Table 1		
Galantamine added $\mu\text{g/ml}$	Haemolysate ChE activity	Serum ChE activity
0	1.00	1.00
1.25	0.96	0.98
2.50	0.86	0.97

The results show a significant reduction of the haemolysate cholinesterase activity with increased concentration of galantamine hydrobromide, whereas the data for the serum activity do not show any statistically significant changes as a response to the addition of the galantamine hydrobromide, which is an indication of a high selectivity of the galantamine hydrobromide with respect to acetylcholinesterase as opposed to butyrylcholinesterase.

Selectivity for acetylcholinesterase in erythrocytes opposed to butyrylcholinesterase is contemplated to reflect the selectivity for acetylcholinesterase at nicotinic receptor sites opposed to the acetylcholinesterase at muscarinic receptor sites.

This test may be used as a screening for candidate cholinesterase inhibitors with respect to their selectivity. However, other tests may be used.

Example 5

Acetylcholinesterase activity in synovial fluid:

Acetylcholinesterase (AcChE) activity was determined in

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synovial fluid from 8 patients with osteoarthritis (OA) and 5 subjects with different Rheumatoid conditions. In each patient synovial fluid was taken from an affected joint by arthrocentesis. Table 2 shows mean values of up to six samples from individual subjects. A broad spectrum of values was seen between these patients, but with a high degree of correspondence between samples taken on different days from the same patient. Samples with high values show bands with AcChE activity on isoelectric focusing gels. It seems that this acetylcholinesterase activity is from free proteins rather than membrane bound simply because of the paucity of lymphocytes seen in the microliter samples.

15

Table 2					
Subject	Age (years)	Condition	AcChE	N	SEM
1 (KJ)	70	OA	16.9	3	3.08
2 (SA)	67	RA	9	1	-
3 (GS)	74	OA	9.6	1	-
4 (SG)	88	OA	7.1	1	-
5 (SR)	41	Menisc	2.1	2	1.15
6 (BG)	50	Menisc	28.9	2	3.95
7 (PJ)	71	OA	3.9	2	1.45
8 (SE)	31	Menisc	22.8	1	-
9 (GV)	75	OA	6.7	5	6.63
10 (SE)	73	OA	1.4	3	0.71
11 (GA)	58	Hydrops	15.3	2	3.7
12 (AL)	70	OA	12.8	6	1.53
13 (SO)	54	OA	23.4	1	-
14 (HG)	62	OA	17.6	3	4.07

- 19 -

Patients numbers 1, 3 and 11 are males, the remaining patients are females.

In patient numbers 1, 6, 7, 11 and 14 samples were taken from the left knee. As for the remaining
5 patients, samples were taken from the right knee.

AcChE = Acetylcholinesterase activity

N = number of measurements

SEM = Standard Error of the Means

10 OA = Osteoarthritis

RA = Rheumatoid Arthritis

Menisc = Lesion of the meniscus

Hydrops = Swollen knee

15 Example 6

Treatment of patients with rheumatoid disease

Ten patients with rheumatoid arthritis were treated with galantamine 10 mg 3 times per day. The purpose of
20 the treatment was to treat their fatigue syndrome resulting from their rheumatoid arthritis. However, it was found that not only did the ten patients improve with respect to their fatigue syndrome, but also in respect of the symptoms of their rheumatoid arthritis
25 condition itself. They spontaneously reported less articular pain and the inflammatory process of their affected joints was less active (as evidenced by less swollen and less painful joints) while they were on treatment with galantamine. Most of the patients have
30 experienced relapse of their symptoms when treatment was interrupted.

Example 7

Treatment of patients with osteoarthritis

35

In a bioavailability study of galantamine in 24 elderly volunteers, 2 volunteers asked to remain on

- 20 -

galantamine at the end of the trial.

The first volunteer, who was already acknowledged by the General Practitioner to be suffering from osteoarthritis, received 10 mg galantamine hydrobromide per day (in the form of 2 x 5 mg doses orally). After seven days, the patient spontaneously reported an improvement in osteoarthritis symptoms. This improvement was maintained over a 31 day period, during which the galantamine hydrobromide dose was raised to 30 mg per day. Symptoms were reported to recur when medication was discontinued.

The second patient, who had been experiencing joint pain for several years, but had not had osteoarthritis diagnosed, also received 10 mg per day galantamine hydrobromide in 2 x 5 mg tablet doses. This patient spontaneously reported an improvement in symptoms after three days of treatment with galantamine.

Example 8

20 Treatment of a patient with anaemia of chronic disorder

A 61 years old woman with Rheumatoid Arthritis had for 3 years suffered from anaemia which did not respond to conventional therapy.

25 The patient received 15 mg galantamine hydrobromide per day (in the form of 3 x 5 mg doses orally). After 14 days, the laboratory blood tests reflecting anaemia showed significant improvement as shown in Table 3. The patient was treated in the period between 3 January 1997 and 20 January 1997.

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Table 3			
Normal values	2-12-96	3-1-97	20-1-97
White cells: $3.8-10.2 \times 10^9/L$	6.1	6.6	5.9
Red cells: $4.00-5.8 \times 10^{12}/L$	3.81*	3.72*	3.94
Haemoglobin: 118-158 g/L	118	115*	124
Haematocrit: 0.360-0.470 L/L	0.362	0.342*	0.362
MCV: 81.0-96.0 fl	95.0	91.8	
MCH: 26.5-32.4 pg	31.1	30.9	
MCHC: 323-351	327	336	
RDW: 10.9-15.7	13.25	12.4	
Platelet: 130-370	266	283	

Two weeks' treatment with galantamine 15 mg per day apparently raised haemoglobin to 124, the highest value in three years, and also improved considerably other clinical signs and symptoms.

* = abnormal values

Example 9

Treatment of patients with rheumatoid diseases

13 patients suffering from different arthritic disorders of rheumatoid origin received galantamine tablets 2.5 mg 3 times per day for 1 week followed by 5 mg 3 times per day for the next four weeks. After the 5 weeks of treatment the patients reported the following differences in symptoms as shown in Table 4.

- 22 -

Table 4						
Tab. Galantamine HBr, 5 mg						
Effect in patients with rheumatological diseases						
Subject	Age	Condition	Pain	Concentration	Memory	Stiffness
1 (EB)	60	RA	d	u	u	d
2 (GT)	63	OA	d	i	i	d
3 (GA)	34	OA (mild)	d	i	i	u
4 (GG)	40	Post. inf. a.	u	u	u	u
5 (GR)	(50?)	SLE	d	u	u	
6 (GS)	(40?)	Spond	u	u	u	u
7 (IG)	48	Spond	u	u	u	u
8 (MG)	52	Spond	u	u	u	u
9 (RB)	60	Poly/RA	d	u	u	u
10 (SEB)	39	Poly/RA	d	u	u	u
11 (SO)	62	Poly	u	u	u	u
12 (PT)	30	Pso. a.	d	i	i	d
13 (UJ)	60	Poly	u			u

Patient numbers 4 and 12 are males, the remaining patients are females. Age is measured in years, age in brackets reflect approximate age.

OA = Osteoarthritis
 RA = Rheumatoid Arthritis
 Post Inf. a. = Arthritis after infection
 SLE = Systematic Lupus Erythematosus
 Spond = Ankylosing Spondilitis
 Poly = Polyarthritis
 Pso. a. = Arthritis associated with psoriasis
 u = unaffected
 d = decreased
 i = increased (corresponding to at least 50% improvement)

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Stiffness: Joint stiffness is a complaint covering sensations which range from slight resistance to all movements through the normal range, to blocking of certain movements due to fixed anatomical changes.

5 Certain types of stiffness are highly characteristic, such as early morning stiffness.

10 Early morning stiffness occurs primarily in rheumatoid arthritis, but also in other arthritic diseases. The patient awakes with distressing, painful stiffness of all affected joints. This is gradually "worked off" by activity over one half to three hours or more. This "limbering up time" provides a reliable measure of inflammatory activity. In osteoarthritis stiffness tends to come on later in the day and is
15 preceded by activity.

In one of the examples given of rheumatoid patients on galantamine, the parameters evaluated were tiredness, sleep, pain and stiffness. In one RA patient (patient number 1) the grip strength was evaluated and proved to
20 augment over 50%. All these parameters were evaluated with a questionnaire and VAS (Visual Analogue Scale) which refer to the patients' reporting as regards the severity of the symptoms, represented by a 0-100 percentage line.

25 As appears from Table 4, 50% of the patients (patient numbers 1, 2, 3, 5, 9, 10 and 12) reported a significant improvement in their symptoms.

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CLAIMS:

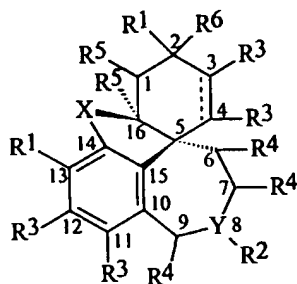
1. The use of a pharmaceutically acceptable cholinesterase inhibitor or a pro-drug therefor in the manufacture of a medicament for combatting diseases associated with proteolytic enzyme activity.
2. The use as claimed in claim 1 wherein the cholinesterase inhibitor blocks or inhibits protease activity or protease production.
3. The use as claimed in claim 1 or claim 2 wherein the disease is psoriasis.
4. The use as claimed in claim 1 or claim 2 wherein the disease is an inflammatory bowel disease.
5. The use as claimed in claim 4 wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.
6. The use as claimed in claim 1 or claim 2 wherein the disease is selected from osteoarthritis, rheumatoid arthritis and other forms of arthritis.
7. The use as claimed in any one of the preceding claims wherein the cholinesterase inhibitor is an acetyl cholinesterase inhibitor.
8. The use as claimed in any one of the preceding claims wherein the cholinesterase inhibitor is active substantially selectively at nicotinic receptor sites.
9. The use as claimed in any one of the preceding claims wherein the cholinesterase inhibitor is capable of crossing the blood brain barrier.

- 25 -

10. The use as claimed in any one of claims 1 to 7
 wherein the cholinesterase inhibitor is selected from
 physostigmine, tacrine and tacrine analogues, fasciculin,
 metrifonate, heptyl-physostigmine, norpyridostigmine,
 5 norneostigmine, huperazine, donepezil and pro-drugs of
 any of these.

11. The use is claimed in any one of claims 1 to 9
 wherein the cholinesterase inhibitor is selected from
 10 glantamine, epigalantamine and norgalantamine, and
 analogues, salts and derivatives of any of these.

12. The use as claimed in any of the preceding claims
 wherein the cholinesterase inhibitor is selected from
 15 galantamine and its derivatives of formula (I):



25

wherein the broken line represents an optionally present
 double bond between carbon atoms 3 and 4, each R_1 is
 independently selected from hydrogen, hydroxyl, straight
 30 or branched chain alkyl, hydroxyalkyl, carboxyalkyl
 amino, alkylamino, acyl, lower alkanoyl, cyano,
 sulfhydryl, C_{1-6} alkoxy, alkylthio, aryloxy, arylthio, R_3 -
 substituted aryloxy, R_3 -substituted arylthio, aralkoxy,
 an optionally R_3 -substituted aliphatic or aryl carbamyl
 35 group, aralkylthio, R_3 -substituted aralkoxy, R_3 -
 substituted aralkylthio, aryloxymethyl, R_3 -substituted
 aryloxymethyl, alkanoyloxy, hydroxy-substituted

- 26 -

alkanoyloxy, benzoyloxy, R_3 -substituted benzoyloxy, aryloxycarbonyl and R_3 -substituted aryloxycarbonyl,

R_2 is selected from hydrogen, straight or branched chain C_{1-6} alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R_3 -substituted phenyl, alkylphenyl, R_3 -substituted alkylphenyl, heterocyclyl selected from α - or β -furyl, α - or β -thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R' -substituted heterocyclyl, where R' is alkyl or alkoxy,

each R_3 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R_4 is independently selected from hydrogen, halo, trifluoromethyl or C_{1-4} -alkyl,

each R_5 is independently selected from hydrogen or hydroxymethyl,

R_6 is hydrogen or C_{1-6} alkyl, or when R_1 at carbon atom 2 is hydroxyl, R_6 may be a moiety of formula I wherein R_6 is hydrogen and R_1 is a linking bond; or

R_1 at carbon atom 2 and R_6 may jointly form semicarbazone,

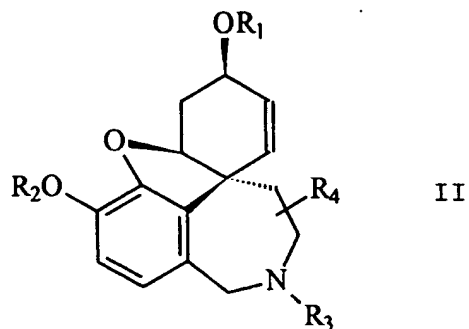
X is oxygen or NR_3 ,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and pharmaceutically acceptable acid addition salts thereof.

13. The use as claimed in any one of the preceding claims wherein the cholinesterase inhibitor is selected from compounds of formula II

- 27 -



15 wherein R¹ and R² which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

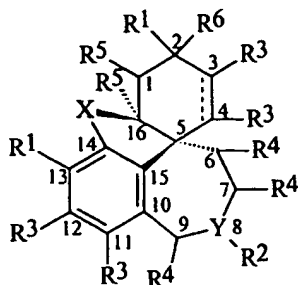
20 R³ is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and R⁴ represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton, and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

25

14. The use according to any one of the preceding claims where the cholinesterase inhibitor is galantamine or a salt thereof.

30 15. The use of galantamine or a derivative thereof of formula I:

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wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R_1 is independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, C_{1-6} alkoxy, alkylthio, aryloxy, arylthio, R_3 -substituted aryloxy, R_3 -substituted arylthio, aralkoxy, an optionally R_3 -substituted aliphatic or aryl carbamyl group, aralkylthio, R_3 -substituted aralkoxy, R_3 -substituted aralkylthio, aryloxymethyl, R_3 -substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_3 -substituted benzoyloxy, aryloxycarbonyl and R_3 -substituted aryloxycarbonyl,

R_2 is selected from hydrogen, straight or branched chain C_{1-6} alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R_3 -substituted phenyl, alkylphenyl, R_3 -substituted alkylphenyl, heterocyclyl selected from α - or β -furyl, α - or β -thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R' -substituted heterocyclyl, where R' is alkyl or alkoxy,

each R_3 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl,

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aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy,
alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino,
N-arylamino, N-alkaryl amino, fluoro, chloro, bromo,
iodo, and trifluoromethyl,

5 each R_4 is independently selected from hydrogen,
halo, trifluoromethyl or C_{1-4} -alkyl,

each R_5 is independently selected from hydrogen or
hydroxymethyl,

10 R_6 is hydrogen or C_{1-6} alkyl, or when R_1 at carbon
atom 2 is hydroxyl, R_6 may be a moiety of formula I
wherein R_6 is hydrogen and R_1 is a linking bond; or

R_1 at carbon atom 2 and R_6 may jointly form
semicarbazone,

X is oxygen or NR_3 ,

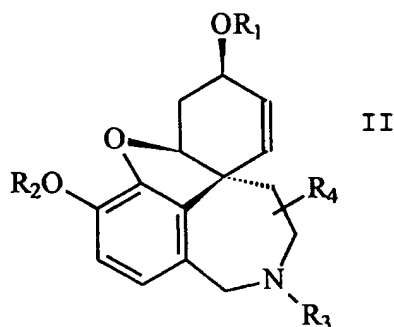
15 Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and
pharmaceutically acceptable acid addition salts thereof
in the manufacture of a medicament for combatting
diseases associated with proteolytic enzyme activity.

20

16. The use of galantamine or a derivative thereof of
formula II

25



30

wherein R^1 and R^2 which may be the same or different
each represents a hydrogen atom or an acyl group, such
35 as a lower alkanoyl group, e.g. an acetyl group or a
straight-chained or branched alkyl group, e.g. methyl,
ethyl, propyl, or isopropyl;

- 30 -

R³ is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl,

5 heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

R⁴ represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton,

10 and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide in the manufacture of a medicament for combatting diseases associated with proteolytic enzyme activity.

15 17. The use of galantamine or a salt thereof in the manufacture of a medicament for combatting diseases associated with proteolytic enzyme activity.

20 18. A method of combatting diseases associated with proteolytic enzyme activity comprising administering a pharmaceutically acceptable cholinesterase inhibitor or a pro-drug therefor.

25 19. A method as claimed in claim 18 wherein the disorder is as defined in any one of claims 2 to 6.

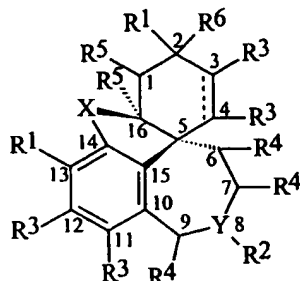
20. A method as claimed in claim 18 or claim 19 wherein the cholinesterase inhibitor is as defined in any one of claims 7 to 14.

30

21. The use of a pharmaceutically acceptable cholinesterase inhibitor or a prodrug therefor in the manufacture of a medicament for combatting psoriasis.

35 22. The use as claimed in claim 21 wherein the cholinesterase inhibitor is defined in any one of claims 7 to 14.

23. The use of galantamine or a derivative thereof of formula I:



wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R_1 is independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, C_{1-6} alkoxy, alkylthio, aryloxy, arylthio, R_3 -substituted aryloxy, R_3 -substituted arylthio, aralkoxy, an optionally R_3 -substituted aliphatic or aryl carbamyl group, aralkylthio, R_3 -substituted aralkoxy, R_3 -substituted aralkylthio, aryloxymethyl, R_3 -substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_3 -substituted benzoyloxy, aryloxycarbonyl and R_3 -substituted aryloxycarbonyl,

R_2 is selected from hydrogen, straight or branched chain C_{1-6} alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R_3 -substituted phenyl, alkylphenyl, R_3 -substituted alkylphenyl, heterocyclyl selected from α - or β -furyl, α - or β -thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R' -substituted heterocyclyl, where R' is alkyl or alkoxy,

- 32 -

each R_3 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkaryl amino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R_4 is independently selected from hydrogen, halo, trifluoromethyl or C_{1-4} -alkyl,

each R_5 is independently selected from hydrogen or hydroxymethyl,

R_6 is hydrogen or C_{1-6} alkyl, or when R_1 at carbon atom 2 is hydroxyl, R_6 may be a moiety of formula I wherein R_6 is hydrogen and R_1 is a linking bond; or

R_1 at carbon atom 2 and R_6 may jointly form semicarbazone,

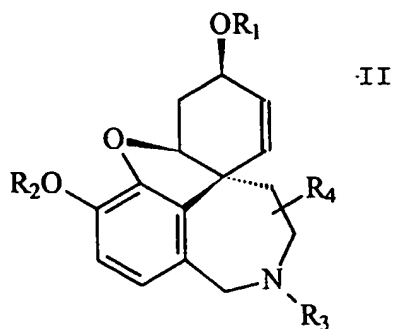
X is oxygen or NR_3 ,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and pharmaceutically acceptable acid addition salts thereof

in the manufacture of a medicament for combatting psoriasis.

24. The use of galantamine or a derivative thereof of formula II



wherein R^1 and R^2 which may be the same or different each represents a hydrogen atom or an acyl group, such

- 33 -

as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

5 R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

10 R^4 represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton,

and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide in the manufacture of a medicament for
15 combatting psoriasis.

25. The use of galantamine or a salt thereof in the manufacture of a medicament for combatting psoriasis.

20 26. A method of combatting psoriasis comprising administering a pharmaceutically acceptable cholinesterase inhibitor or a pro-drug therefor.

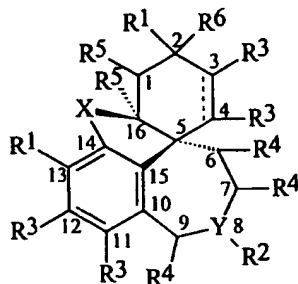
25 27. A method as claimed in claim 26 wherein the cholinesterase inhibitor is as defined in any one of claims 7 to 14.

30 28. The use of a pharmaceutically acceptable cholinesterase inhibitor or a prodrug therefor in the manufacture of a medicament for combatting osteoarthritis, rheumatoid arthritis or other forms of arthritis.

35 29. The use as claimed in claim 28 wherein the cholinesterase inhibitor is defined in any one of claims 7 to 14.

- 34 -

30. The use of galantamine or a derivative thereof of formula I:



- 35 -

each R_3 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R_4 is independently selected from hydrogen, halo, trifluoromethyl or C_{1-4} -alkyl,

each R_5 is independently selected from hydrogen or hydroxymethyl,

R_6 is hydrogen or C_{1-6} alkyl, or when R_1 at carbon atom 2 is hydroxyl, R_6 may be a moiety of formula I wherein R_6 is hydrogen and R_1 is a linking bond; or

R_1 at carbon atom 2 and R_6 may jointly form semicarbazone,

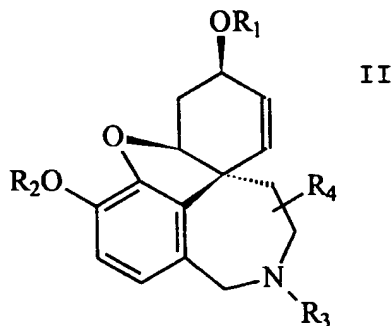
X is oxygen or NR_3 ,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and pharmaceutically acceptable acid addition salts thereof

in the manufacture of a medicament for combatting osteoarthritis, rheumatoid arthritis or other forms of arthritis.

31. The use of galantamine or a derivative thereof of formula II



wherein R^1 and R^2 which may be the same or different

- 36 -

each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

5 R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

10 R^4 represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton,

 and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or
15 methiodide in the manufacture of a medicament for combatting osteoarthritis, rheumatoid arthritis or other forms of arthritis.

32. The use of galantamine or a salt thereof in the
20 manufacture of a medicament for combatting osteoarthritis, rheumatoid arthritis or other forms of arthritis.

33. The use of a pharmaceutically acceptable
25 cholinesterase inhibitor or a prodrug therefor in the manufacture of a medicament for the treatment of rheumatoid diseases.

34. The use of a pharmaceutically acceptable
30 cholinesterase inhibitor or a prodrug therefor in the manufacture of a medicament for the treatment of rheumatoid diseases such as Juvenile Arthritis, Systemic Lupus Erythematosus, Sjögren's Syndrome, Progressive Systemic Sclerosis, Polymyositis, Dermatomyositis,
35 Ankylosing Spondylitis, Reiter's Syndrome, Psoriatic Arthritis, Relapsing Polychondritis, Relapsing Panniculitis, Crohn's Disease, Ulcerative Colitis,

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Hereditary Complement Deficiencies, Collagen Vascular Diseases, Felty's Syndrome, rheumatological manifestations associated with bacterial and viral endocarditis or myocarditis and other rheumatological manifestations such as anaemia of chronic disorders.

35. The use of a pharmaceutically acceptable cholinesterase inhibitor or a prodrug therefor in the manufacture of a medicament for the treatment of anaemia associated with chronic disorders.

36. The use as claimed in any one of claims 33 to 35 wherein the cholinesterase inhibitor is as defined in any one of claims 7 to 14.

15

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02448

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/27 A61K31/66 A61K31/44 A61K31/445 A61K31/40
A61K31/645 A61K31/435 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 97 29750 A (SNORRASON ERNIR ;MURRAY JAMES (GB)) 21 August 1997 see the whole document ---	1-36
P, X	WO 98 00119 A (BOEHRINGER INGELHEIM KG ;WESSLER IGNAZ (DE); BOEHRINGER INGELHEIM) 8 January 1998 see the whole document ---	1-5, 7-10, 18-22, 26, 27, 33, 34, 36
X	"SHIRE TO DOUBLE UK PRODUCT SALES" DIALOG FILE SUPPLIER: FILE 129:PHIND (ARCHIVAL); AN=537410 & SCRIP 2234, 23 May 1997, page 10 XP002086644 see the whole document ----- -/-	1, 2, 6-9, 11-20, 28-33, 36



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

3 December 1998

Date of mailing of the international search report

21/12/1998

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Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02448

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"SHIRE PHARMACEUTICALS AND JANSSEN BUY OUT NIVALIN RIGHTS" DIALOG FILE SUPPLIER: FILE 129: PHIND (ARCHIVAL); AN=539896 & SCRIP 2240, 13 June 1997, page 8 XP002086645 see the whole document	1,2,6-9, 11-20, 28-33,36
X	DIALOG FILE SUPPLIER: FILE 187: F-D-C REPORTS; AN=192079 & THE PINK SHEET, vol. 59, no. 32, 11 August 1997, XP002086646 see the whole document	1,2,6-9, 11-20, 28-33,36
X	DIALOG FILE SUPPLIER: FILE 187: F-D-C REPORTS; AN=154052 & THE TAN SHEET, vol. 4, no. 27, 1 July 1996, XP002086647 see the whole document	1-3,7-9, 11-27
X	US 4 661 509 A (GORDON ARNOLD Z ET AL) 28 April 1987 see the whole document	1,2, 7-10, 18-20, 33-36
X	GB 1 491 679 A (GALLARDO ANTONIO SA) 9 November 1977 see the whole document	1,2,6-9, 18,19, 28,29, 33,34,36
X	US 5 229 401 A (EFFLAND RICHARD C ET AL) 20 July 1993 see abstract see column 5, line 44 - column 7, line 42 see column 12, line 32 - line 41; claims	1-3,7-9, 18-22, 26,27, 34,36
A	T.G. DIMITROV: "EFFECT OF THE PSYCHOSTIMULANT MESOCARB ON THE ANTIINFLAMMATORY AND ANALGESIC ACTIVITY OF NIVALIN" DOKLADY BOLGARSKOI AKADEMII NAUK, vol. 42, no. 9, 1989, pages 115-118, XP002086648 see the whole document	1-36

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/ 02448

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-20, 26, 27
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 18-20, 26, 27
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.